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Original article

Depressive symptoms are common and associated with adverse clinical outcomes in heart failure with reduced and preserved ejection fraction

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ABSTRACT

Background: Little is known about depressive symptoms in heart failure with preserved ejection fraction (HFpEF, EF ≥50%). We aimed to assess the prevalence of depression, to clarify the impact of depressive symptoms upon clinical outcomes, and to identify factors associated with these symptoms in HF with reduced EF (HFrEF, EF <50%) and HFpEF.

Methods and results: A total of 106 HF outpatients were enrolled. Of them, 61 (58%) had HFpEF. Most patients were male (HFrEF 80%, HFpEF 70%) and the mean of plasma B-type natriuretic peptide (BNP) level in the HFrEF group was similar to that in the HFpEF group (164.8 ± 232.8 vs. 98.7 ± 94.8 pg/mL). HFrEF patients were treated more frequently with beta-blockers compared with HFpEF patients (71% vs. 43%, $p = 0.004$). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D). The prevalence of depression (CES-D score ≥16), and CES-D score did not significantly differ between HFrEF and HFpEF (24% vs. 25%, 14.1 ± 8.3 vs. 12.1 ± 8.3, respectively). During the 2-year follow-up, depressed patients had more cardiac death or HF hospitalization in HFrEF (55% vs. 12%, $p = 0.002$) and HFpEF (35% vs. 11%, $p = 0.031$). Cox proportional hazard analysis revealed that a higher CES-D score, indicating increased depressive symptoms, predicted cardiac events independent of BNP in HFrEF [hazard ratio (HR) 1.07, 95% confidence interval (CI) 1.01–1.13] and HFpEF (HR 1.09, 95%CI 1.04–1.15). Multiple regression analyses adjusted for BNP showed that independent predictors of depressive symptoms were non-usage of beta-blockers and being widowed or divorced in HFrEF. On the other hand, usage of warfarin was the only independent risk factor for depressive symptoms in HFpEF (all, $p < 0.05$).

Conclusions: Depressive symptoms are common and independently predict adverse events in HFrEF/HFpEF patients. This study suggests that beta-blockers reduce depressive symptoms in HFrEF. In contrast, treatment for depression remains to be elucidated in HFpEF.

Introduction

Heart failure (HF) imposes one of the highest disease burdens compared to any medical condition in Japan, with an estimated 1.3 million outpatients experiencing HF in 2030 [1]. The risk for developing HF increases with advancing age, and HF is one of the most frequent causes of hospitalization [2].

HF has been traditionally classified with systolic and diastolic HF, although these should not be considered as separate entities, as most HF patients have both systolic and diastolic dysfunction at rest or with exercise. Diastolic HF has also been described as HF with preserved ejection fraction (HFpEF). The prevalence of HFpEF has increased over time compared to HF with reduced EF (HFrEF) [3]. Such changes may be due to the demographic shift caused by the aging population, and the evolution of more sophisticated therapeutic strategies for HF. Patient characteristics differ between HFrEF and HFpEF groups. Those affected by the latter have been older and more often women, and are more likely to have underlying hypertension [3–5]. Despite these differences, the prognosis of HFpEF has been shown to be poor, with outcomes similar to those for HFrEF in Japan as well as Western countries [3,4].

Depressive disorder is a common healthcare problem in HF. The prevalence rate of clinically significant depression among HF patients was 21.5% in a meta-analysis of 27 studies, and the

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prevalence rates reported across these studies ranged from 9% to 60% [6]. Studies including our own have shown that symptoms of depression are independent risk factors for adverse clinical outcomes among HF patients [7–10]. However, most of these studies targeted HF patients with systolic dysfunction. The prevalence of depression and its effect on clinical outcomes in HFpEF remains to be fully elucidated. Given the increases in HFpEF and its poor prognosis, depressive symptoms in HFpEF should receive immediate attention.

Several clinical trials have investigated the effects of depression treatment in patients with cardiovascular disease including HF [11,12]; however, these studies failed to find concrete evidence. Considering the pathophysiological differences between HFrEF and HFpEF and the fact that established therapy for HFrEF does not necessarily provide beneficial effects in HFpEF patients [13], the treatment strategy for depression may also differ between HFrEF and HFpEF. Identifying factors contributing to depressive symptoms could help health professionals to determine the optimal medical approach for reducing depressive symptoms, and thereby improve clinical outcomes among HFrEF and HFpEF patients.

Therefore, the purpose of this study was (1) to assess the prevalence of depression, (2) to clarify the impact of depressive symptoms upon clinical outcomes, and (3) to identify factors associated with these symptoms in HFrEF and HFpEF patients.

Methods

Patients and study design

This study was a prospective, observational study of HF outpatients. The institutional review board of University of Tokyo approved this study (No. 1445 and 1445-1). All participants provided informed consent. The details of the study design have been described previously [9,14]. All consecutive HF outpatients who were making scheduled visits to the cardiovascular outpatient clinic of the University Hospital in Tokyo between July 2006 and November 2006 were enrolled. The attending physician determined whether each patient met our criteria based on medical records and the patient symptoms.

Patients were included when they were diagnosed with HF in accordance with Framingham HF criteria [15] and were at least 20 years of age. Exclusion criteria were the physical inability to complete the questionnaire, or inability or unwillingness to give informed consent. We excluded HF patients with etiology of valvular heart diseases in cases where they had not been hospitalized due to worsening of HF as well as cases where the current severity of valvular heart disease was trivial or mild. We also excluded two patients receiving hemodialysis, because we considered that the number of hemodialysis patients in the study was not enough to evaluate impacts of hemodialysis on depressive symptoms, given the fact that hemodialysis may be closely associated with other clinical and psychological status [16].

In this study, patients with left ventricular EF (LVEF) of $\geq$50% were classified as having HFpEF, whereas those with LVEF of <50% were classified as having HFrEF [3]. LVEF was assessed using ultrasound cardiography.

Patients were followed up for a median period of 2.1 years, and they received usual care from their primary care physicians and/or cardiologists.

Endpoints

The primary endpoint was the composite endpoint of cardiac death or hospitalization due to worsening of HF. Hospitalization for HF was defined as an admission primarily diagnosed with HF. The information on endpoints was collected from medical records. We also mailed a follow-up letter to all patients or their family approximately 2 years after the initial assessment to enquire about the patients' clinical outcomes. If the requested information was not received within 4–6 weeks after mailing, we asked the attending physicians about the clinical outcomes.

Depressive symptoms

Depressive symptoms were measured using the Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D) [17,18]. CES-D is a 20-item self-report questionnaire designed for the screening of depressive symptoms on a four-point Likert scale ranging from 0 to 3. The scores for each item are summed to give a range of total scores from 0 to 60. A higher score indicates a greater tendency toward depressive symptoms. A total score of $\geq$16 indicates the presence of clinically significant depression, and thus we classified patients with scores of $\geq$16 as suffering from depression. CES-D has previously been used in patients with HF [6,19]. Semantic equivalence of the Japanese version of CES-D with the original English version has been ascertained by means of back translation. Validity and reliability of CES-D Japanese version have also been confirmed as described previously [9,18]. In the Japanese version, the cut-off value of 16 was also optimal [9,18].

Measures

The following clinical information was collected from medical records at baseline: etiology of HF; duration of HF; prior hospitalizations for HF; New York Heart Association (NYHA) functional class; B-type natriuretic peptide (BNP); LV end-diastolic diameter by ultrasound cardiography; systolic/diastolic blood pressure; heart rate; atrial fibrillation including paroxysmal atrial fibrillation; hemoglobin concentration; estimated glomerular filtration rate (GFR) (calculated using the Japanese formula [20], i.e. estimated GFR = $194 \times \text{age}^{-0.287} \times \text{creatinine}^{-1.094}$ [and, if female, $\times 0.739$]); diabetes mellitus; and medication including β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and/or angiotensin II receptor blockers (ARBs), warfarin, and antidepressants and/or anti-anxiety drugs.

We asked patients to complete a self-administered questionnaire to assess demographic and clinical characteristics. This questionnaire included gender, age, marital status, educational level, employment, living situation, and CES-D.

Statistical analysis

Categorical data are presented as frequencies and percentages. For continuous variables with a normal distribution, the mean and standard deviations are reported. For variables not normally distributed, the median and inter-quartile ranges (IQR) are reported. Kaplan–Meier curves were developed to examine the unadjusted relationship of depression with the endpoints, using the log-rank test for statistical comparison. Cox proportional hazard models were used to assess the relationship between depressive symptoms and the endpoints after adjustment for log BNP. The logarithmic BNP was included in the model by forced entry, as a measure to assess the severity of HF.

To identify variables related to depressive symptoms, a univariate analysis was initially performed. The dependent variable was the CES-D score, and independent variables were demographic and clinical characteristics. Pearson's product–moment correlation coefficient or Spearman's rank-correlation coefficient was calculated for continuous variables. The Student *t*-test or the Mann–Whitney *U*-test was used to evaluate differences between the two groups. One-way analysis of variance was also used to

compare the score between the three groups. After assessing the multicollinearity, a multiple regression analysis with adjustment for logarithmic BNP was conducted. Variables that were related to depressive symptoms at $p < 0.10$ in the univariate analysis were entered into the model. They were then selected using the backward method (the significance level required for retention in the model was 0.20).

All statistical tests were two-tailed, and statistical significance was defined as $p < 0.05$. All analyses were performed with SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

A total of 115 patients participated in the survey. Nine patients were excluded for the following reasons: 2 patients did not return the questionnaire, more than 80% of all items were missing in the questionnaire of 6 patients, and the medical data of 1 patient were not available at baseline. Thus, 106 patients were included in the final analysis. The effective response rate was 92.2%. Characteristics of patients were not different between study patients and those not included in the study.

Demographic and clinical characteristics of the study patients are shown in Table 1. Fifty-eight percent of study patients had HFpEF. The mean age at baseline was 61 years in the HFrEF group and 67 years in the HFpEF group. Most patients were male (HFrEF 80%, HFpEF 70%) and married (HFrEF 73%, HFpEF 70%). The median of plasma BNP level in the HFrEF group was similar to that in the HFpEF group (65 pg/mL vs. 71 pg/mL, respectively). The prevalence rate of atrial fibrillation did not significantly differ between HFrEF and HFpEF groups (29% vs. 36%, respectively). HFrEF patients were treated more frequently with β-blockers compared with HFpEF patients (71% vs. 43%, respectively; $p = 0.004$). Among those who

Table 1
Baseline characteristics of study patients.

	HF with reduced EF ($N = 45$)	HF with preserved EF ($N = 61$)	p-Value
Depressive symptoms			
The CES-D score ≥16	11(24%)	15(25%)	0.986
The CES-D score	14.1 ± 8.3	12.8 ± 8.3	0.439
Demographic characteristics			
Gender, male	36(80%)	43(70%)	0.267
Age, years	61.1 ± 16.4	66.5 ± 15.4	0.084
Marital status			
unmarried	6(13%)	10(16%)	0.909
married	33(73%)	43(70%)	
divorced or widowed	6(13%)	8(13%)	
Education, >12 years	19(42%)	28(46%)	0.706
Employment, employed	19(42%)	28(46%)	0.706
Living-alone	5(11%)	8(13%)	0.756
Current smoker	9(20%)	5(8%)	0.076
Clinical characteristics			
Etiology of HF			0.015
Ischemic	17(38%)	17(28%)	
Cardiomyopathy	19(42%)	13(21%)	
Valvular heart disease	2(4.4%)	13(21%)	
Hypertension	2(4.4%)	6(9.8%)	
Congenital heart disease	5(11%)	8(13%)	
Others or unknown	0(0%)	4(6.6%)	
Duration of HF, years	1.7 (0.9–3.9)	3.5(1.6–6.5)	0.050
Prior hospitalization for HF	30(67%)	25(41%)	0.009
NYHA functional class			0.288
I	8(18%)	19(31%)	
II	29(64%)	32(52%)	
III	8(18%)	10(16%)	
BNP, pg/mL	164.8 ± 232.8	98.7 ± 94.8	0.406
Median (IQR)	65.0(35.3–187.3)	70.9(29.0–134.5)	
LVEF, %	38.7 ± 8.1	60.9 ± 7.4	<0.001
LVDd, mm	59.6 ± 6.8	49.9 ± 6.6	<0.001
Systolic BP, mmHg	123.2 ± 22.8	126.3 ± 20.1	0.469
Diastolic BP, mmHg	71.6 ± 13.5	70.5 ± 10.2	0.656
Heart rate, beats/min	72.1 ± 12.6	70.3 ± 12.5	0.481
Atrial fibrillation			0.541
Persistent	11(24%)	16(26%)	
Paroxysmal	2(4.4%)	6(9.8%)	
Hemoglobin, g/dL	13.4 ± 2.5	13.0 ± 2.0	0.299
Estimated GFR, mL/min/1.73 m^2	60.4 ± 24.3	61.5 ± 18.8	0.806
Estimated GFR<60	24(53%)	31(51%)	0.798
Diabetes mellitus	17(38%)	20(33%)	0.594
Medication			
β-Blockers	32(71%)	26(43%)	0.004
ACEIs and/or ARBs	33(73%)	39(64%)	0.306
Digoxins	14(31%)	16(26%)	0.581
Diuretics	36(80%)	35(57%)	0.014
Warfarin	16(36%)	30(49%)	0.162
Antidepressants and/or Anti-anxiety drugs	5(11%)	2(3.3%)	0.132

HF, heart failure; EF, ejection fraction; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; BP, blood pressure; GFR, glomerular filtration rate; ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers. Depression symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), a higher score represents having more depressive symptoms. Patients with CES-D score of 16 or greater was considered those with depression. Values are n (%), mean ± standard deviation, or median (inter-quartile range).

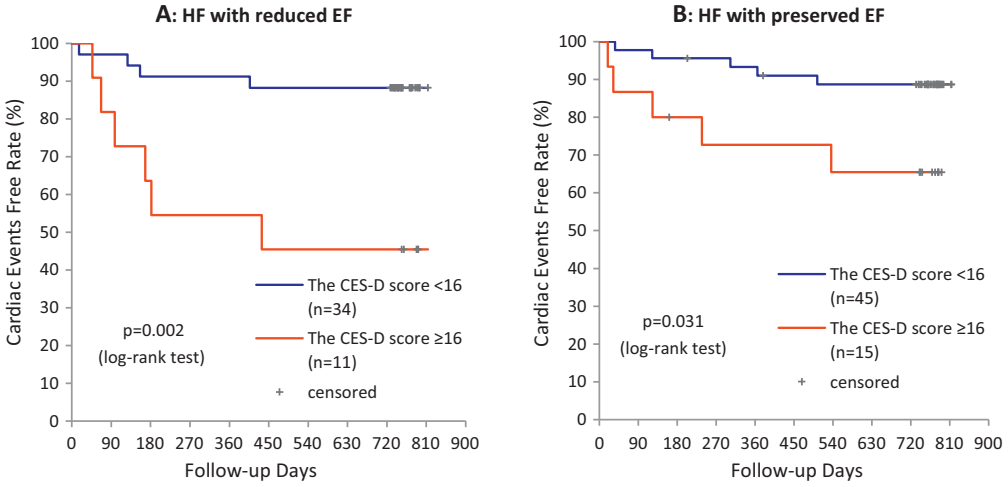

Fig. 1. Kaplan–Meier curves for cardiac event-free survival according to depression, defined as Center for Epidemiologic Studies Depression Scale (CES-D) score of ≥16. Cardiac events represent cardiac death or hospitalization for heart failure. HF, heart failure; EF, ejection fraction.

were taking β-blockers, carvedilol was prescribed to 97% in HFrEF and 81% in HFpEF.

Overall, 11 (24%) HFrEF patients and 15 (25%) HFpEF patients scored ≥16 on CES-D and thus were classified as depressed. There was no significant difference in the CES-D score between HFrEF and HFpEF groups (14.1 ± 8.3 vs. 12.8 ± 8.3, respectively). Five (11%) HFrEF patients and 2 (3.3%) HFpEF patients were taking antidepressants and/or anti-anxiety drugs.

The relationship of depressive symptoms with adverse clinical outcomes

Of 106 patients, vital status data were available in 105 patients. The median days of follow-up was 756 (2.1 years; IQR, 732–738). During the follow-up period, 10 (22%) patients in HFrEF and 10 (17%) patients in HFpEF either died from cardiac cause or were hospitalized for HF at least once. The cumulative 1- and 2-year composite endpoint rates were 18% and 22% in HFrEF, and 14% and 17% in HFpEF, respectively.

Compared with non-depressed patients, depressed patients defined as having a CES-D score of ≥16 had higher rates of cardiac death or HF hospitalization, not only for those with HFrEF [12% vs. 55%, $p = 0.002$; hazard ratio (HR) 5.87; 95% confidence interval (CI) 1.65–20.9, $p = 0.006$; Fig. 1A], but also for those with HFpEF (11% vs. 35%; $p = 0.031$; HR 3.60, 95% CI 1.04–12.5, $p = 0.043$; Fig. 1B). Table 2 shows the results of Cox proportional hazard analysis. A higher CES-D score, indicating increased depressive symptoms, was strongly associated with an increased risk of the composite endpoint in HFrEF (HR 1.07; 95% CI 1.01–1.13; $p = 0.023$; HR for each 1-point change in total score on the CES-D scale) and HFpEF (HR 1.09; 95%CI 1.04–1.15; $p = 0.001$) groups. After adjustment of the log BNP value, depressive symptoms were still associated with adverse cardiac events, irrespective of LVEF ($p = 0.033$ in HFrEF, $p = 0.013$ in HFpEF; Table 2).

The 1-and 2-year mortality rates were 6.7% and 11.3% in HFrEF patients and 3.6% and 9.0% in HFpEF patients, respectively. None of the patients died from suicide. A Kaplan–Meier survival analysis showed that mortality from any cause in depressed patients was greater than that for non-depressed patients with HFrEF (48% vs. 0%; $p < 0.001$). Whereas mortality was not significantly different between patients with and without depression in HFpEF (15% vs. 11%; $p = 0.547$). As shown in Table 2, a higher CES-D score was significantly associated with an increased risk of mortality in the HFpEF group (HR 1.08; 95% CI 1.01–1.15; $p = 0.025$) as well as in the HFrEF group (HR 1.14; 95% CI 1.06–1.23; $p < 0.001$). Depressive symptoms remained predictive of mortality after adjustment of BNP levels in the HFrEF group ($p = 0.002$).

Factors associated with depressive symptoms

Table 3 compares the CES-D score between the two or three populations stratified by various patient characteristics. In the HFrEF group, living alone and marital status were predictive of depressive symptoms. Tukey's multiple comparisons found that patients who were widowed or divorced experienced significantly more depressive symptoms than HFrEF patients who were married ($p < 0.05$). Non-usage of β-blockers as well as ACEIs and/or ARBs was also associated with having more depressive symptoms in the HFrEF group (all, $p < 0.05$). As for HFpEF, there was a significant positive relationship between the log BNP level and depressive symptoms. HFpEF patients who had persistent atrial fibrillation experienced more depressive symptoms than patients who did not have atrial

Table 2
Relationship of depressive symptoms with adverse clinical outcomes.

	HF with reduced EF ($N = 45$)			HF with preserved EF ($N = 60$)		
	HR	(95% CI)	*p*-Value	HR	(95% CI)	*p*-Value
Cardiac death or hospitalization for HF						
Unadjusted	1.07	(1.01–1.13)	0.023	1.09	(1.04–1.15)	0.001
Adjusted for BNP level	1.08	(1.01–1.15)	0.033	1.08	(1.02–1.14)	0.013
All-cause mortality						
Unadjusted	1.14	(1.06–1.23)	<0.001	1.08	(1.01–1.15)	0.025
Adjusted for BNP level	1.25	(1.08–1.45)	0.002	1.07	(0.994–1.16)	0.070

HF, heart failure; EF, ejection fraction; HR, hazard ratio; CI, confidence interval; BNP, B-type natriuretic peptide. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), a higher score represents more having depressive symptoms.

Table 3
Univariate predictors of depressive symptoms.

		HF with reduced EF ($N=45$)	p-Value	HF with preserved EF ($N=61$)	p-Value
Gender	Female	18.0 ± 10.1	0.111	13.8 ± 9.2	0.535
	Male	13.1 ± 7.6		12.4 ± 8.0	
Age, years		0.276	0.066	0.074	0.573
Marital status	Unmarried	13.3 ± 5.9	0.011	8.8 ± 4.5	0.107*
	Married	12.5 ± 7.0		14.2 ± 9.0	
	Divorced or widowed	23.2 ± 11.8		10.1 ± 5.6	
Education	>12 years	13.1 ± 8.9	0.488	12.6 ± 8.8	0.867
	≤12 years	14.8 ± 7.8		13.0 ± 8.0	
Employment	Employed	12.3 ± 8.6	0.229	12.2 ± 7.2	0.614
	Unemployed	15.3 ± 8.0		13.3 ± 9.2	
Living-alone	Yes	21.4 ± 12.1	0.034	9.8 ± 4.0	0.072
	No	13.2 ± 7.4		13.3 ± 8.7	
Current smoker	Yes	13.9 ± 4.7	0.919	11.6 ± 5.4	0.738
	No	14.1 ± 9.0		12.9 ± 8.5	
Ischemic etiology of HF	Yes	14.6 ± 8.7	0.718	13.1 ± 6.3	0.856
	No	13.7 ± 8.2		12.7 ± 9.0	
Duration of HF, years		0.045	0.767	−0.083	0.526
Prior hospitalization for HF	Yes	13.3 ± 8.4	0.406	12.8 ± 9.6	0.998
	No	15.5 ± 8.0		12.8 ± 7.4	
NYHA functional class	I	12.4 ± 2.0	0.758	10.8 ± 4.8	0.159
	II	14.1 ± 9.7		12.7 ± 8.7	
	III	15.5 ± 6.3		17.0 ± 11.1	
Log BNP, pg/mL		0.239	0.115	0.338	0.008
LVEF, %		−0.156	0.308	0.031	0.811
LVDd, mm		0.197	0.199	−0.218	0.094
Systolic BP, par 10 mmHg		0.218	0.151	−0.212	0.102
Diastolic BP, par 10 mmHg		0.151	0.323	−0.133	0.308
Heart rate, beats/min		0.014	0.927	0.061	0.638
Atrial fibrillation					
Persistent	Yes	15.7 ± 9.6	0.552	17.7 ± 12.2	0.006*
Paroxysmal	Yes	9.0 ± 9.9		15.7 ± 2.7	
	No	13.8 ± 7.8		10.4 ± 5.6	
Hemoglobin, g/dL		−0.194	0.203	−0.028	0.831
Estimated GFR	≥60	13.2 ± 8.9	0.535	11.6 ± 8.3	0.255
mL/min/1.73 m^2	<60	14.8 ± 7.7		14.0 ± 8.3	
Diabetes mellitus	Yes	15.8 ± 9.0	0.271	11.0 ± 6.0	0.177
	No	13.0 ± 7.7		13.7 ± 9.1	
Medication					
β-blockers	Yes	12.3 ± 7.1	0.021	11.9 ± 7.1	0.460
	No	18.5 ± 9.5		13.5 ± 9.1	
ACEIs and/or ARBs	Yes	12.6 ± 7.6	0.043	13.3 ± 9.2	0.532
	No	18.2 ± 8.9		11.9 ± 6.4	
Digoxins	Yes	16.4 ± 9.7	0.215	13.1 ± 12.9	0.918
	No	13.0 ± 7.4		12.7 ± 6.1	
Diuretics	Yes	14.6 ± 9.0	0.185	12.7 ± 8.7	0.899
	No	11.9 ± 4.0		13.0 ± 7.9	
Warfarin	Yes	14.9 ± 9.4	0.632	15.2 ± 9.6	0.027
	No	13.6 ± 7.7		10.5 ± 6.1	
Antidepressants	Yes	23.4 ± 12.9	0.144	22.0 ± 4.2	0.111
and/or Anti anxiety drugs	No	12.9 ± 6.9		12.5 ± 8.2	

HF, heart failure; EF, ejection fraction; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; BP, blood pressure; GFR, glomerular filtration rate; ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers. Depression symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), a higher score represents having more depressive symptoms. Patients with CES-D score of 16 or greater was considered those with depression. Values are mean ± standard deviation, Pearson's product–moment correlation coefficient, or Spearman's rank-correlation coefficient.

* $p < 0.05$ by the Tukey's multiple comparisons: married vs. divorced or widowed; no presence of atrial fibrillation vs. persistent atrial fibrillation.

fibrillation after analysis with Tukey's multiple comparison ($p < 0.05$). Usage of warfarin was also predictive of depressive symptoms in HFpEF. On the other hand, usage of β-blockers as well as ACEIs and/or ARBs was not related to depressive symptoms in HFpEF.

Table 4 shows the results of the multiple regression analysis adjusted for log BNP level. Because there was a significant relationship between marital status and living alone ($p < 0.001$), we used the variables of marital status instead of living alone in multivariate analyses. Independent predictors of more depressive symptoms were non-usage of β-blockers and being widowed or divorced in HFrEF patients (standard partial regression coefficients [sβ] = −0.301, $p = 0.030$; sβ = 0.425, $p = 0.003$, respectively) and usage of warfarin in HFpEF patients (sβ = 0.253, $p = 0.038$).

Discussion

We found that depression was common (24% in the HFrEF group and 25% in the HFpEF group) and the prevalence did not differ among the two groups experiencing different systolic functions. To our knowledge, this is the first Japanese study to demonstrate that an increase in depressive symptoms is associated with adverse cardiac events independently of HF severity, not only in those with HFrEF but also in those with HFpEF. An exploratory analysis designed for a better understanding of depressive symptoms showed that the independent risk factors for depressive symptoms were non-usage of β-blockers and being widowed or divorced in the HFrEF group, and usage of warfarin in the HFpEF group. These findings highlight the need for screening depressive symptoms

Table 4
Multivariate modeling of depressive symptoms.

	Parameter estimate	sβ	*p*-Value
HF with reduced EF (*N* = 45)			
Usage of β-blockers	−5.43	−0.301	0.030
Married status			
Divorced or widowed vs. married	10.22	0.425	0.003
Unmarried vs. married	2.81	0.117	0.408
R^2 (Adjusted R^2)		0.323	(0.255)
HF with preserved EF (*N* = 60)			
Usage of warfarin	4.19	0.253	0.038
LVDd, mm	−0.23	−0.182	0.131
R^2 (Adjusted R^2)		0.220	(0.178)

HF, heart failure; EF, ejection fraction; sβ, standard partial regression coefficients; LVDd, left ventricular end-diastolic diameter. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), a higher score represents more having depressive symptoms. Log BNP level was entered into the multivariate model forcedly. After we assessed the multicollinearity, variables that were related to the depressive symptoms at $p < 0.10$ in univariate analysis (Table 3) were entered into the model. Then the variables were selected by backward methods ($p < 0.20$).

among HF patients irrespective of LVEF and suggest that HF treatment strategies for depressive symptoms may differ according to systolic function.

Prevalence of depression

The prevalence of depression among those with HFpEF has not yet been determined in a definitive manner for this disorder. Our study revealed that about a quarter of patients had depression defined as having a CES-D score of ≥16 in the HFpEF group as well as in the HFrEF group. This prevalence rate is similar to the results obtained from a meta-analysis in HF [6], and is 2–3 times higher compared with that in the general population [21]. Because the relationship between depression and HF is based on a complex pathophysiology, it is still unclear whether depression has a causal effect on the development of HF or whether it is a symptom of HF syndrome. However, our results indicate the need to improve depressive symptoms in HFpEF and HFrEF patients.

Depressive symptoms and clinical outcomes

Interestingly, we found that co-morbid symptoms of depression are risk factors for adverse cardiac events in HFrEF and HFpEF patients, and this trend was remarkable in HFrEF. These results expand findings from previous investigations [7–10]. A meta-analysis of 8 studies has found that HF patients with heightened depressive symptoms or depressive disorder had a 2-fold increased risk of death and associated clinical outcomes [6]. However, most patients included in the meta-analysis had HFrEF. Our studies reaffirm the importance of co-morbid symptoms of depression as an independent predictor of prognosis in HFpEF and HFrEF patients.

Various reasons for this observed increased risk of adverse clinical outcomes and depressive symptoms have been proposed. Depression may contribute to poor prognosis through adverse effects on health behaviors including non-adherence of prescribed treatment plans [19,22,23]. Several pathophysiologic pathways have also been identified in HFrEF. Depression has been shown to be related to decreased heart rate variability, blunted baroreflex sensitivity, heightened sympathetic nervous system activity, blood hypercoagulability, increased inflammation, and endothelial dysfunction in HFrEF [19,22,23]. Each of these pathways has been associated with poor outcomes and may act independently or synergistically to increase risk in HFrEF. Most of these pathways may be commonly shared in HFpEF, but further studies are necessary to clarify this point.

Factors associated with depressive symptoms

The identification of HF patients with depressive symptoms is important because of the association between depression and adverse outcomes. Knowing the risk factors for depressive symptoms may facilitate the treatment. Interestingly, usage of β-blockers was associated with fewer symptoms of depression in HFrEF patients. As described above, depression shares a common pathophysiology with HFrEF [19], i.e. HFrEF is clearly accompanied by high neurohormonal activation, with norepinephrine and renin–angiotensin–aldosterone. In depression, sympathetic nervous system hyperactivity is associated with overstimulation of the hypothalamic–pituitary–adrenal (HPA) axis [19,22,23]. In view of the similarities of these neurohormonal alterations, lipophilic β-blockers such as carvedilol that have been established to be efficacious in HFrEF could alleviate symptoms of depression by reducing hyperactivity of the HPA axis by passing thorough the blood–brain-barrier. In this study, a univariate analysis also showed that usage of ACEIs and/or ARBs was associated with fewer symptoms of depression in HFrEF patients. Taking these observations into consideration, ACEIs and/or ARBs as well as β-blockers may be able to confer beneficial effects on HFrEF patients with depressive symptoms. However, further research is necessary to confirm these indications. In contrast, we observed no significant association of depressive symptoms with usage of β-blockers, ACEIs and/or ARBs in HFpEF patients, which is similar to findings that these drugs did not have a clear impact on clinical outcomes in HFpEF [13].

Being widowed or divorced was also associated with having more depressive symptoms in HFrEF patients, which is consistent with a prior study showing that the death of a loved one worsens depressive symptoms [24]. Emotionally stressful events, including loss, can trigger pure adrenergic stimulation and increased circulation of cytokines, such as tumor necrosis factor-alpha and interleukin-6 [22], and cytokine levels may also increase in patients with depression [22]. Because of the high neurohormonal activation and the increased levels of cytokines in HFrEF patients, emotional stress may facilitate the development of depressive symptoms in HFrEF patients. Having a spouse is often an indication of the highest available level of social support, which has been shown to be an important factor in reducing depressive symptoms and in improving survival [24,25]. Clarifying the specific needs of patients who are widowed or divorced and then identifying and reinforcing current social support networks could be helpful in improving depressive symptoms in HFrEF patients.

With respect to HFpEF patients, usage of warfarin was an independent risk factor for having more depressive symptoms. Although well-controlled anticoagulation with warfarin could

potentially prevent the strokes related to atrial fibrillation and heart valve replacement, the therapeutic range for anticoagulants is narrow [26,27]. To maintain this narrow target range, patients require frequent monitoring and dose adjustment. Numerous barriers to the use of warfarin have also been reported: regular visits to the clinic, dietary restrictions for foods that contain vitamin K, and anxiety regarding potential hemorrhagic events and possible drug interactions [28,29]. These difficulties associated with warfarin can potentially reduce the quality of life and increase depressive symptoms [29]. Meta-analyses have shown that self-testing and self-management of oral anticoagulation reduce thromboembolic events and improve survival [26,27]. Psychoeducational support in the patients taking warfarin may be able to reduce depressive symptoms, although it is not feasible for all patients. Regarding HFrEF patients, usage of warfarin was not related to depressive symptoms. It may be because HFrEF patients without warfarin had depressive symptoms similar to those with warfarin, suggesting an importance to provide depression treatment and care tailored to patient's needs in HFrEF with or without warfarin.

We observed that usage of antidepressants and/or anti-anxiety drugs was likely to result in more depressive symptoms in HFrEF and HFpEF patients. However, because the study was not designed to assess impacts of the drugs, the significance of this observation is unclear. From previous studies, selective serotonin reuptake inhibitors seem to be a safer choice for the treatment of depressed HF patients, but the long-term effects on HF prognosis remains to be confirmed [30]. The recent SADHART-CHF trial that tested sertraline has not shown any beneficial effect on either cardiovascular or all-cause mortality in HFrEF patients [12]. Thus, the current optimal treatment therapy for HF itself and psychoeducational support incorporates the fundamental approach of reducing depressive symptoms and improving clinical outcomes in HF patients and depressive symptoms.

Study limitations

Our study has several potential limitations. First, the clinical diagnosis of depression cannot be made with CES-D, which has been shown to be a reliable and valid instrument for measuring depressive symptoms [17,18]. Second, the generalizability of this study was limited because all patients were recruited from a cardiovascular outpatient clinic at a single university hospital in Tokyo. Third, hemodialysis patients were excluded in this study. Further study is necessary to evaluate impacts of hemodialysis on depressive symptoms and clinical outcomes in HF patients. Forth, a cross-sectional assessment of variables including depressive symptoms and usage of β-blockers cannot confirm a causative relationship. Fifth, the small sample size and low frequency of adverse events in this study limited the number of variables examined in multivariate analyses and the statistical significance of our findings. Finally, depressive symptoms were assessed only at baseline. Using only one snapshot assessment may miss the true nature of these symptoms in a given individual. The relationship between the change in depressive symptoms and subsequent clinical outcomes needs to be investigated in future research.

Conclusions

This study has revealed that the prevalence of depression is 24% in HFrEF patients and 25% in HFpEF patients, suggesting that depression is common, irrespective of LVEF. It has also demonstrated that increased symptoms of depression are associated with an increased risk of adverse cardiac events, independent of HF severity in HFrEF and HFpEF patients. To better understand treatment and care for patients with HF and depressive symptoms, we have explored factors associated with these symptoms. Independent predictors for experiencing more depressive symptoms are non-usage of β-blockers and being widowed or divorced in the HFrEF group and usage of warfarin in the HFpEF group. These findings suggest that β-blocker therapy reduces depressive symptoms in HFrEF. In contrast, treatment for depression remains to be elucidated in HFpEF.

Disclosures

None.

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